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Review

Mast cells in airway diseases and interstitial lung disease

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ABSTRACT

Mast cells are major effector cells of inflammation and there is strong evidence that mast cells play a significant role in asthma pathophysiology. There is also a growing body of evidence that mast cells contribute to other inflammatory and fibrotic lung diseases such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. This review discusses the role that mast cells play in airway diseases and highlights how mast cell microlocalisation within specific lung compartments and their cellular interactions are likely to be critical for their effector function in disease.

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1. Introduction

Mast cells are highly specialised granulocytes that contribute towards innate and adaptive immunity (Echtenacher et al., 1996) as well as tissue repair and revascularisation (Heissig et al., 2005; Iba et al., 2004; Weller et al., 2006). Mast cells perform the majority of their functions by releasing preformed and/or newly generated pleiotropic mediators in response to diverse activation signals to trigger a programmed inflammatory response. Mast cells

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are present in all vascularised tissues and are particularly abundant at sites of the environmental interface, such as the skin, gastrointestinal tract and the pulmonary epithelia. Thus mast cells are well equipped to respond to their environment where they can trigger an inflammatory response against a perceived tissue insult. Indeed, mast cells appear to be able to "sense" their environment by extending membranous projections into the lumen of blood vessels, which can sensitise the cells to respond to antigen (Cheng et al., 2013). However, in many disease states such as asthma, chronic inflammation may be due to inappropriate mast cell activation and/or redistribution of mast cells to specific structures that could drive detrimental tissue remodelling processes contributing to disease progression. In fact, mast cells are found to be in an "activated" state in asthmatic airways (for review see Bradding et al. (2006)) suggesting that either the tissue microenvironment is supporting chronic mast cell activation or mast cells in asthmatic airways are intrinsically hyper-secretory. Despite asthma being associated with atopy, the role of allergen exposure in chronic asthma may be overstated and the disease can become self-perpetuating once established. Indeed, mast cells may also play roles in other respiratory diseases that are not associated with atopy, such as chronic obstructive pulmonary disease (COPD) and interstitial lung diseases, where the drivers of mast cell involvement are often idiopathic, but unlikely to be allergens. In this review, we will discuss current opinion on the role that mast cells play in airway diseases with particular emphasis on asthma where the role of mast cells is more understood.

2. Mast cell heterogeneity

Mast cells are long-lived tissue-resident cells derived from haematopoietic stem cells that leave the bone marrow as mast cell-committed, but undifferentiated $CD34^+$ progenitor cells. Mast cell precursors are recruited into tissues where they become resident and then mature and differentiate under the influence of the local cytokine milieu (for review see Gurish and Boyce (2006)). Therefore, mast cells represent heterogeneous populations depending upon the tissue where they reside and the local cytokine environment. For example, human lung mast cells can be discriminated from mast cells isolated from other tissues based on their profile of released mediators and surface expression of chemokine receptors (Bradding et al., 1995; Brightling et al., 2005b; Irani et al., 1991; Oskeritzian et al., 2005; Saito et al., 2006; Weidner and Austen, 1993). This heterogeneity also extends to the microlocalisation of mast cells within distinct tissue compartments (Bradding, 2009). Thus, human mast cells from different lung compartments contain granules with distinct protease content, which can be classified as mast cells containing either tryptase only (MC_T), chymase only (MC_C) or both tryptase and chymase (MC_{TC}) in their granules (Balzar et al., 2005; Bradding et al., 1995; Weidner and Austen, 1993).

The MC_T subtype is smaller and contains less histamine than the MC_{TC} subtype (Oskeritzian et al., 2005; Schulman et al., 1983, 1990) and it is possible that MC_{TC} development from MC_T cells may be a step in maturation. However, it is clear that mast cells can change subtype in response to their environment and that changes in subtype can occur in both directions. For example, MC_{TC} cells cultured with human airway epithelial cells convert to an MC_T phenotype *in vitro* (Hsieh et al., 2005), whereas MC_T cells cultured with endothelial cells transform into an MC_{TC} phenotype (Mierke et al., 2000). This phenomenon most likely also occurs *in vivo* since the MC_T subtype predominates in the lung parenchyma, bronchial lamina propria and bronchial epithelium, while the MC_{TC} subtype surrounds pulmonary blood vessels with close proximity to the vascular endothelial cells (Andersson et al., 2009; Bradding et al., 1995; Irani et al., 1989, 1991). The significance and consequences of microlocalisation of mast cell subtypes is not yet clear and the factors that drive the development of each subtype are largely unknown and most likely multifactorial. However, these observations demonstrate the complexity of the mast cell compartment and the heterogeneity of mast cell populations that can adapt to a changing environment.

3. Mechanisms that support mast cell growth and function

Many canonical mast cell functions are regulated by two distinct, but interconnected receptor-mediated signalling pathways. Mast cells regulate adaptive immune responses when they encounter antigen that crosslinks immunoglobulin E (IgE) bound to the high affinity IgE receptor, FcεRI (for review see Rivera and Gilfillan (2006)). Aggregation of FcεRI triggers a number of signalling pathways that lead to the release of Ca^{2+} from intracellular stores, influx of extracellular Ca^{2+} and reorganisation of the cytoskeleton that are all critical processes for the release of pre-stored and newly generated mediators (Allen et al., 2009; Cruse et al., 2013; Draber et al., 2012; Gilfillan and Beaven, 2011; Gilfillan and Tkaczyk, 2006; Hajkova et al., 2011; Rivera and Gilfillan, 2006). Mast cells can also respond to a variety of alternative stimuli that may inhibit or augment FcεRI-dependent responses. One of the most important crosstalk interactions between receptors may be the synergism between FcεRI and KIT, the receptor tyrosine kinase for stem cell factor (SCF) encoded by the proto-oncogene *c-KIT* (for reviews see Cruse et al. (2014), Gilfillan and Tkaczyk (2006) and Lennartsson and Ronnstrand (2012)). SCF is the major growth and survival factor for mast cells and is absolutely required for mast cell survival (Jensen et al., 2007; Okayama and Kawakami, 2006). In addition, SCF is a chemoattractant for mast cells (Halova et al., 2012; Okayama and Kawakami, 2006) and synergistically enhances antigen-induced degranulation, cytokine production and migration (reviewed in Gilfillan and Tkaczyk (2006)). Therefore, increased concentrations of SCF in tissues may not only promote mast cell recruitment, survival and differentiation, but could also result in increased mast cell responsiveness. As will be discussed below, SCF expression in the airways of patients with asthma has been reported to be increased compared to control subjects (Al-Muhsen et al., 2004; Da Silva et al., 2006) and therefore may play an important role in asthma pathogenesis and contribute to low-level chronic activation of mast cells. Indeed, under certain circumstances where either the actin cytoskeleton (Smrz et al., 2013) or inhibitory molecules such as SH2 domain containing inositol-5-phosphatase-1 (SHIP-1) that interact with the actin cytoskeleton (Gimborn et al., 2005; Lesourne et al., 2005) are perturbed, SCF does not simply potentiate mast cell degranulation, but can directly induce degranulation (Huber et al., 1998; Smrz et al., 2013).

It is clear that SCF has the capacity to regulate most mast cell functions, which highlights the importance of understanding the signalling mechanisms that control specific functional responses to SCF. The mechanisms that regulate whether mast cells will differentiate or proliferate in response to SCF, for example, are not well understood. It is possible that the concentration of SCF and/or differential phosphorylation of specific tyrosine residues in KIT may play roles in dictating responses, although studies to specifically address these possibilities are needed. SCF also plays important roles in mast cell adhesion to structural cells where SCF exists as a membrane bound form (Hollins et al., 2008; Koma et al., 2005; Wygrecka et al., 2013). Most studies of SCF function in mast cells have been performed with the soluble form of SCF, which would be expected to undergo endocytosis more rapidly than a membrane tethered ligand. While studies on the membrane